MEDICAL REVIEWERS REPORT

BLA SUPPLEMENT 97-0501

PRODUCT: Proleukin (aldesleukin), Proleukin, Interleukin-2 (IL-2)

INDICATION: Treatment of metastatic melanoma

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SPONSOR: Chiron Corporation

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ABBREVIATIONS USED:

- OR: objective response
- CR: complete response
- PR: partial response
- NCI: National Cancer Institute
- MM: metastatic melanoma
- RCC: (metastatic) renal cell carcinoma
- AE: adverse event SAE: serious adverse event
- PFS: progression free survival
- NR: non-responder

Study protocol numbers were used in shortened versions

- T86-0063 =0063
- 92C-0094=0094
- T90-0053=0053
- T86-0097=0097
- T86-0170=0170
- T84-0524=0524
- C87-0002=70002
- CS-L291-06=29106

Study patients were listed by last 4 numbers of patient ID if there were > 4 digits.

SECTION I - BACKGROUND

Melanoma

Melanoma constitutes 3% of all cancers occurring in humans. Over the last two decades, the rate of melanoma has increased by approximately 6% per year. It is predicted there will be over 40,000 new cases of melanoma/year by the year 2000. The death rate is also rising by 2% annually. In 1997 it is estimated there will be 7,300 deaths from melanoma. The lifetime risk is 1/87 (1/70 for males).

Melanoma is staged either by the extent and depth of primary lesions (Breslow thickness), and the presence of regional, nodal, or distant metastases (AJCC system grades I-IV). Prognosis of patients with stage IV (metastatic) disease has remained stable over the last 20 years (Appendix one). Table 1 below and Appendix 1 display data on 1275 patients treated at the [redacted] who were staged using the current (AJCC) system. (b)(4)

Other than stage of disease, there remain a limited number of prognostic factors which correlate with survival. In stage III disease the number of involved lymph nodes containing tumor is the single most important prognostic factor. Prognosis for stage III disease is the same whether or not the primary site has been identified, if the study is stratified by number of involved nodes. For stage IV (distant metastatic disease) those with soft tissue have a better prognosis than those visceral metastases (Table 1).

Other factors which have been correlated with improved survival include female gender, good performance status, and a single metastatic site

Table 1. Survival in melanoma by stage of disease[1]

Location	5 yr survival	10 yr survival	15 yr survival	Median Survival
Regional LN (AJCC Stage III)	46%	41%	38%	
Unknown Primary-LN (AJCC Stage III or IV)	46%	41%		37 months
Distant metastases (Stage IV)	6%			7.3 months
Skin, SC				11 months
Lung				10 months
GI,CNS				4 months
Single site metastasis				7-12 months
Multiple sites of metastases				2-8 months

SC are subcutaneous: LN is lymph node: CNS is central nervous system

Alternative treatment for metastatic melanoma

DTIC (dimethyl triazeno imidazole carboxamide, Dacarbazine™) is the only product approved for the treatment of metastatic melanoma. The results in a series of large, multicenter trials enrolling a total of 580 patients between 1972 and 1976 which utilized single agent DTIC or a DTIC-based combination chemotherapy regimen were published in 1984.[i] The overall (12-20%) and complete (3-6%) response rates for each individual study are similar; the authors pooled the data for all 580 patients, which yielded an overall response rate of 19% (110/580) and a complete response rate of 4.5% (26/580). The median duration of response for patients achieving CR is reported to be 58 weeks, with a range of 7 to 296+

[1] Data are taken from the chapter on Melanoma in, Cancer Medicine, 3rd edition, edited by Holland, James F., Frei, Emil III, et al. Chapter XXXIV, pages 1793-1824. Blank cells indicate data were not available.

weeks. At the time of the publication, there were six patients continuing in complete remission at 78, 94, 121, 216, 285 and 296 weeks.
The finding that estrogen receptors were expressed in malignant melanoma led to investigations of Tamoxifen as an active agent in this disease. A review of the experience of phase 2 studies, enrolling a total of 213 patients, yielded an overall response rate of 7%; data from this overview suggested that the response rate might be higher in postmenopausal women. [ii] This finding was further evaluated by the EORTC in phase II study enrollling 102 evaluable postmenopausal women with metastatic melanoma. The CR rate in this study was 1% with a 5% overall response rate. Responses were observed primarily in women with non-visceral disease.

Objective responses have been reported with a variety of nitrosoureas. The largest experience with single agent nitrosourea therapy was a study of conducted in 226 patients treated with fotemustine. The overall response rate (25%) is similar to that reported with other agents in the class; the complete response rate was 3%. Of note, responses were reported in visceral sites and in the central nervous system.

Additional single agents shown to have modest activity in melanoma , primarily in single center, phase 2 studies, are cisplatin, paclitaxel, docetaxol, and interferon alfa. For each of the agents, the overall and complete response rates are low (table below) with short durations of response.

Regimens combining several active agents have been studied since the 1980's. Two common combination regimens are the Dartmouth regimen (DTIC, cisplatin, BCNU, and tamoxifen) and BOLD (bleomycin, Oncovin, lomustine and DTIC). Initial reports noted high overall response rates with complete response rates of 10-15% and prolonged remission durations. With additional experience across different centers, the high overall and complete response rates have been reproduced, however, durable, long term responses are uncommon, with median CR durations of 3-15 months for BOLD and 15 months for the Dartmouth regimen now observed.[iii]

Table 2. Single Agent and Combination Chemotherapy Regimens for Treatment of Melanoma

Agent	CR Rate	ORR	Median CR duration
DTIC†	4.5% (26/580)	19% (84/580)	58 weeks
Tamoxifen	2% (5/213)	7% (15/213)	
Tamoxifen‡	1% (1/102)	5% (5/102)	
Fotemustine	3% (7/226)	25% (57/ 226)	
Paclitaxel		18% (12/65)	
Docetaxol	4% (1/26)	15% (4/26)	15 months
Cisplatin	0-6%	10-26%	
Interferon alfa	5% (18/380)	16% (60/380	
BOLD	15%	45%	3-15 months
DTIC/BCNU/DDP/TAM	14% (55/384)	44% (170/384)	15 months

† DTIC single agent or in combination other agents
‡ study restricted to postmenopausal women

SECTION TWO-INTERLEUKIN-2 BACKGROUND

Biology of IL-2

Interleukin-2 (IL-2) is a lymphokine produced by normal T lymphocytes and initially described in 1976. It is a member of the class of polypeptide autocrine and paracrine growth factors that regulate immune responses. It is central to both cellular and humoral arms of the immune system and regulates lymphocyte proliferation and differentiation. After exposure to plant lectins, antigens or other stimuli IL-2 is produced by the CD4+ T cells, and a subset of CD8+ cells. To initiate IL-2 secretion, a ligand on B cells has to interact with the CD28 receptor on the T cell. IL-2 can induce proliferation of T-cells independently

(autocrine).IL-2 is a hydrophobic glycoprotein with a molecular weight of 15,600 daltons. Recombinant IL-2 differs from native IL-2[

6 lines

]

Approval of aldesleukin for renal cell carcinoma(RCC)

Aldesleukin was licensed in 1992 for the treatment of metastatic renal cell cancer. The licensed dose of aldesleukin is 600,000 IU/kg administered every 8 hours intravenously over 15 minutes for 5 days for a maximum of 14 doses (cycle 1). Following a rest period of 6-10 days, a second 5 day cycle is administered. A course consists of two cycles with a maximum of 28 IL-2 doses/course recommended. In clinical studies leading to licensure, patients received a median of 20 doses during the first course of therapy (maximum of 28 doses) and one to three courses were administered. (b)(4)

Among 255 patients with metastatic renal cell carcinoma the overall response rate was 15% with 7% CR (17/255) and 8% PR (20/255). With continued follow-up through 1996, the median PR duration was 20.3 months while the median duration of CR has not been reached. Continued tumor regression has been observed more than 12 months after the last dose of aldesleukin. Patients with more favorable ECOG performance status at initiation of therapy were more likely to experience tumor responses and less likely to experience serious toxicity. Experience in patients of ECOG PS 2 is extremely limited.

There were 11/255 aldesleukin- related deaths (4%). At one week after therapy for RCC,14% of patients remained hospitalized due to complications. Persistent nonfatal toxicities included 2 cases of myocardial infarction , 2 cases of renal failure requiring dialysis, 5 cases requiring laparotomy, 6 cases requiring intubation for > 1 week, 2 cases of gangrene requiring surgery and a CVA. Eighty-five percent of patients had hypotension, 52% dyspnea, 73 % mental state changes, and 64% elevated bilirubin as drug-related toxicities.

Proposed indication

"Proleukin is also indicated for the treatment of adults (> or equal to 18 years of age) with metastatic melanoma". The proposed dosage and administration for metastatic melanoma would be identical to the approved dose and schedule for the treatment of metastatic renal cell carcinoma.

SECTION THREE-CLINICAL STUDIES

Overview

The results of eight studies were pooled and integrated into a single database. All eight studies utilized an IV bolus or short intravenous infusion of IL-2 rather than continuous infusion and all eight employed a similar dosing pattern. Studies 0524 and 29106 were phase 1-2 studies, study 0094 was a treatment protocol, and the remainder were phase 2. Four protocols were NCI intramural programs conducted at the NIH Clinical Center , three were extramural studies which included the Surgery Branch of the NCI (2 multi-institutional and one single study site). The last study was sponsored by Chiron. All eight studies collected both safety and tumor response data.

Auditing and Monitoring

The data collected during the conduct of the trials were contained in three electronic databases. These electronic data records served as the primary data source. In addition , Chiron verified the database information for all patients categorized as responders and all long term survivors. Chiron audited the objective responses using a uniform set of criteria for CR and PR and audited all patients who did not complete the first 30 days of dosing for any reason. Safety audits were done on over half of the 147 intramural patients (protocols 0094, 0097, 0053 and 0524), on all patients in protocol 70002, on 16 of

73 patients in the Cytokine Working Group Study (0170), and on the 5 patients in Chiron study 29106. Case records were compared to a single page follow-up data sheet distributed to investigators and case files were found on all but three audited cases. Radiologic films were missing on four patients; radiologic reports were used to evaluate response.

Chiron audited the primary records to confirm all objective tumor responses, using the definitions below. Nine patients originally designated as responders were changed to non-responders by the sponsor. One CR was changed to a PR. Ten duration of responses were shortened, and one was increased. The original protocols do not provide a specific monitoring schedule; however AE and tumor response data were routinely collected . Followup of all patients classified as responders and any patient with long term survival was conducted through the third quarter of 1996.

Response criteria CR required total disappearance of all tumor for at least 2 consecutive observations taken at least 28 days apart. PR required a 50% or greater reduction in the sum of the total tumor burden for at least 28 days. The tumor burden was measured as the sum of the products of the largest diameter and its perpendicular diameter for each lesion. Individual lesions which increased in size did not disqualify a PR unless the increase was documented on two sequential measurements taken at least 28 days apart. Stable disease was defined as <50% decrease in total tumor burden and <25% increase in total tumor burden or in any individual lesions. Progressive disease was defined as a 25% increase in any individual lesion or the sum of the total tumor burden on 2 sequential measurements 28 days apart. Response duration and progression-free survival were censored at the time of a second intervention. Duration of response was measured from the date of the PR or CR (best response in the sponsors database) to the date of disease progression. Survival was assessed as the time from first dose to death. Progression free survival was assessed from the time of the first dose to disease progression.

Description of the Clinical Studies

Overall goals Exploration of the use of IL-2 therapy for treatment of malignant melanoma and other solid tumors was initiated in 1985 and ended in 1993. The eight phase 1 and 2 studies focused on route, pattern of administration, and dosing . The studies also dealt with management of serious adverse events and determined IL-2 "activity" in shrinking tumor metastases. There were limited efforts to determine sample size in preparation for a pivotal study.

Inclusion criteria Inclusion criteria for all studies required that patients have measureable metastatic melanoma which had failed prior therapy, a favorable performance status (ECOG PS 0 or 1) and were expected to survive several months. Normal organ function requirements in the intramural studies were expanded during the trial because of cardiac and pulmonary toxicity observed. Modifications of organ function tests during the conduct of these studies are summarized as follows:

- Study 0054 required a minimum platelet count of 100,000 cells/dL, WBC > 2000 cells/ dL, creatinine < 2.0, bilirubin < 1.5 mg/dL.
- Study 0097only required WBC > 2000
- Study 0053 required creatinine and bilirubin < 1.8
- Study 0094 listed as eligibility criteria only participation in another NCI study protocol.
- Study 0063 expanded the normal organ tests to include FEV > 2 liters or > 75% predicted.
- Study 0170 added to the above a stress treadmill test and no evidence of cardiac problems.
- Study 70002 included all of the above and recommended thallium stress testing. Exclusion criteria were also expanded to preclude patients with brain metastases, active infections, or persons who had received organ allografts or who required steroids.

Dosing and administration schedule. The original intention was to use the same dose of 600,000 IU/kg. Due to pharmacy error, doses of 720,000 IU/kg were given in 4 (n=147) of the 8 studies. Three of the remaining studies received the 600,000 dose and last study received lower doses (table 3). The administration schedule was the same as the recommended schedule for RCC, i.e., a course of two 5 day cycles separated by a rest period of 6-10 days. IL-2 was given every 8 hours by rapid intravenous infusion

or IV bolus. Patients could receive a maximum of 28 doses/course, as tolerated. Stable and responding patients were given additional courses at intervals ranging from 1-3 months. Six studies (0097, 0053,0063, 0170, 70002, 29106) planned to give each patient 1-3 courses; the other two studies did not state the number of planned courses. Dose reduction was not employed; rather IL-2 was withheld for up to two weeks in event of grade 3 or 4 toxicities and restarted only if the toxicity had decreased to a grade 1 or less.

Table 3- Comparative study design and execution

	0524	0097	0053	0094	0063	70002	0170	29106
Study Sponsor Study site(s)	Intramural NCI-NIH	Intramural NCI-NCI	Intramural NCI-NIH NIH	Intramural NCI NIH- NCI	Xmural NCI-U. Md.	Xmural NCI Multiple	Xmural NCI Multiple	Chiron U.Pitt.
Study design	Single arm Dose escal.	2 Arm IL-2 vs IL-2 + LAK	2 Arm IL-2 vs PEG IL-2	Continuing treatment protocol	Single arm IL-2	Single arm IL-2	Single arm IL-2	Single arm IL-2
Dose[1]	720	720	720	720	600	600	600	360 & 540[2]
# of pts	28	84	32	3	9	45	64	5
Phase of study	1, 2	2	2	4	2	2	2	1
Period of study	9/85 to 2/93	4/86 to 8/92	3/90 to 2/91	3/93 to 4/93	4/86 to 12/87	1/88 to 9/90	9/86 to 10/89	7/91 to 8/92
Median total IL-2 dose (MIU/kg)	12.6	14.4	13.7	8.6	11.4	13.8	13.2	16.7
Mean # courses/pt	1.5	1.5	1.0	1.7	1.2	1.0	1.2	2.4

[1] 720 refers to a dose of 720,000 IU/kg and 600 refers to a dose of 600,000 IU/kg: Xmural is extramural
[2] 2 patients received 360,000 and 3 540,000 IU/kg of IL-2

Conduct of the study

Disposition of patients. The disposition of all patients who were registered on the eight studies is provided below. There were 291 patients registered, of whom 270 were eligible and received one or more doses of IL-2 (the efficacy subset). The following reasons were given for ineligibility for 20 patients registered in the intramural studies: apheresis (n=10); assigned to receive LAK cells (n=4); chemotherapy (n=3); limb perfusion (n=6); vaccine therapy (n=3). No details regarding patient characteristics or outcome were given in the application. There was one patient in the extramural studies who never received IL-2; the reason cited was bleeding. Twenty-two patients discontinued treatment prematurely (prior to development of progressive disease); the reasons for early termination are discussed in the Integrated Safety Summary.

TABLE 4 - Disposition of Patients

	Intramural (4 studies)	Extramural (3 studies)	Chiron study
Registered	167	119	5
Ineligible	20	1	0
Eligible[1]	147	118	5

Early terminators[2]	3	17	2

[1]Patients received at least one dose IL-2

[2]Patients terminated from study within 30 days of first IL-2 dose

SECTION FOUR-RESULTS

PATIENT POPULATION The eight studies enrolled a total of two hundred seventy patients. The composition of the patient population was similar across studies (Table 5). There were 30 patients alive as of September, 1996, which included 17 patients who are 5 year survivors. Thirty-nine patients (14%) have been lost to follow-up.

There was a high percentage of subjects with visceral disease and with more than one site of metastatic disease, which are adverse prognostic features. One hundred and eighty six of 270 patients (69%) had visceral lesions. Visceral sites were defined by the sponsor as CNS, liver, lung, adrenal , kidney, spleen , prostate and small bowel sites and non-visceral sites as lymph node, soft tissue, subcutaneous, cutaneous, bone, peritoneum, pleura and other. Seventy-one percent of patients had 2 or more metastatic sites of disease. The majority of patients had clear evidence of distant metastatic disease (stage IV); however for approximately one-quarter of the subjects, there was insufficient information regarding the sites of subcutaneous and/or nodal disease (relative to the primary lesion site) to determine whether any patients with stage IIIc disease were enrolled.

Information on the earlier course of the disease and on responses to prior therapy was limited. Abbreviated clinical histories were submitted only for responding patients. Information regarding stage at diagnosis or at study entry (according to a TNM or AJCC classification) was not captured. The specific sites of disease for cutaneous, subcutaneous and lymphatic metastases were not captured, nor was the site of the primary lesion. Data on prior therapy were available on 269 persons. Most patients had prior surgery; 69 of 269 had chemotherapy and 80 of 270 patients had immunotherapy (table 5). Forty-six percent (123 patients) received systemic therapy, defined as chemotherapy, immunotherapy or hormonal therapy or a combination of these.

Information regarding the comparability of the 8 studies integrated for efficacy evaluation are shown in tables 3 and 5 with respect to (i) study design and execution and (ii) baseline characteristics of the populations enrolled . Table 3 (study design and execution) indicates that studies were started at different times over the 7 year period beginning in 1985. The three NCI, Surgery Branch intramural studies constitute the largest group of subjects (n=144) at a single clinical site. Two of the three studies (protocols 70002 and 0170) were randomized two arm trials comparing bolus IL-2 to IL-2 plus LAK cells or to PEG-IL-2; only IL-2 arm data was used. Two of the extramural studies were at multiple sites utilizing a treatment strategy similar to the intramural studies. Comparison of the cumulative dose and number of doses of IL-2 provides an estimate of the similarity of dose intensity and treatment delivered, although dose administered was driven both by toxicity (dose withheld) and response to treatment. The median number of doses per course was 16.0 for intramural studies and 22 for extramural studies. The median number of courses per patients was 1.4. Table 5 (population features of studies) displays strong similarities between studies with respect to median age, distribution of ECOG performance status, proportion with visceral lesions, and proportion with $\geq$ 2 metastatic sites of disease at study enrty. Study 29106 is an exception. It is hard to interpret because of small numbers. There are some differences in the proportion of patients who had received prior immunotherapy; 25/28 (89.2%) in study 0524, only 24/84 (28.6%) in study 0097, 10/32 (31.3%) in study 0053 and 5/45 (11.1%) in study 70002.

Table 5-Baseline Population Characteristics of Patients in the 8 efficacy studies

	0524	0097	0053	0094	0063	70002	0170	29106	all
Median age (yrs)	44.5	40	39	39	40	44	45.5	38	43.5
Female/male (# pts)	9/19	31/53	10/22	1 /2	5/4	17/28	21/43	2/3	96/174
Number in study	28	84	32	3	9	45	64	5	270
ECOG PS 0	18	70	24	1	8	30	36	4	191 (71%)
PS 1	9	11	7	2	1	15	28	1	74 (27%)
PS 2	1	3	1		0	0	0		5 (2%)
Prior therapy									
Surgery	28	81	30	3	8	na	61	na	211 (78%)
Radiation	1	10	6	1	2	8	11	0	39 (14%)
Chemotherapy	9	20	8	1	0	14	15	2	69 (26%)
Immunotherapy	25	24	10	3	1	5	8	4	80 (30%)
# pts w/Visceral lesions (%)	17 (61)	71(85)	22 (69)	2	2	24 (53)	44 (69)	4	186 (69%)
# pts w/ ≥ 2 sites disease (%)	20 (71)	50(60)	25 (79)	2 (67)	2 (22)	29 (64)	46 (72)	5 (100)	191 (71%)

Figures for ECOG and prior therapy refer to numbers of patients

SECTION FIVE - INTEGRATED EFFICACY RESULTS

Response rates and duration The overall response rate was sixteen percent (43 of 270 subjects). Of these, 17 (6%) were complete responses (CR) and 26 (10%) were partial responses (PR). The median duration of response for all responders (OR) was 8.9 months and 5.9 months for partial responders. The median duration of CR has not been reached.

Table 6 Response rate and Duration

Response category	Resp. Rate	Median Resp duration (mos)	Median PFS (mos)
OR	16% (43/270)	8.9 (1.5 -106+)	13.1 (2.8 - 131+)
CR	6% (17/270)	NR (2.5 - 106+)	NR (7 - 131+)
PR	10% (26/270)	5.9 (1.5 - 92+)	8.3 (2.8 - 95.0+)

NR - median number of events not reached

The response rates across all study centers was similar. All 5 larger studies have comparable overall response rates (13-17%). The CR rate ranged from 2-8% across these 5 centers.

Table 7- Results in 8 studies used to support efficacy

	0524	0097	0053	0094	0063	70002	0170	29106	all
Number in study	28	84	32	3	9	45	64	5	270
OR in %	14	17	16	0	11	13	17	40	16
CR in %	7	7	6.4	0	0	2	8	20	6
PR in %	7	10	9.6	0	11	11	9	20	10

Durability of response. There were long durations of response among the 17 CR patients; 10 of the 17 were ongoing at the time of last followup in 1996 . The individual patient data are seen below and are listed in table 8.

Response status	n	Response duration in months
Ongoing complete responses	10	24.1, 40.5, 41.2, 59.1, 61.9, 65.3, 72.3, 86.3, 102.7, 106.2
Relapsed complete responses	7	2.5, 6.2, 6,4, 8.3, 8.9, 12.9, 18.2

Partial responses were less durable; they are listed in table 11. The table below presents the number and percent of objective remissions lasting over 1, 2, 3, 4 and 5 years. The number of responses of long duration is low and predominantly made up of CR patients.

Response duration

Resp duration (yrs)	# pts in CR	# pts in PR	# pts in CR or PR (%)*
>5	6	1	7 (2.6%)
>4	7	2	9 (3.3%)
>3	9	2	11 (4.1%)
>2	10	3	13 (4.8%)
>1	12	7	19 (7.0%)

* % of study population in sustained CR or PR

Survival As of Sept. 1996, 12 CR and 3 PR patients were alive. The median overall survival is 11.4 months; the median survival of PR. Kaplan-Meier plot of survival is in appendix 2

Patient subgroups	Median Survival (mos)
All patients (n=270)	11.4
Complete responders (n=17)	NR
Partial responders (n=26)	24.3
Non-responders (n=227)	9.7

Timing of response. The median time from initiation of IL-2 to onset of PR was 67 days, with a range of 23 to 241 days, in the 26 patients achieving a PR. The median time from initiation of IL-2 therapy to onset of CR was 133 days with a range of 43 to 897 days. Although the majority of partial responders achieved a PR during treatment, five patients continued to respond after cessation of IL-2, achieving a PR at 1 to 8 months after the last dose of IL-2. Continued, gradual tumor shrinkage after completion of IL-2 therapy was also observed in patients achieving a CR . Data for time to "best response" is found in table 8 for CR and table 9 for PR, and for PR "best and maximum responses" in table 9. In 12 of the 20 evaluable PR patients there was continued shrinkage of tumor by ≥10-20% at the time of maximal response beyond that observed at best response.

Table 8. Complete Responders: Response duration, time to response, # and distribution of metastatic sites

Pt. ID#	Response duration	Time to "best" response (days)	Lung	Liver	lymph Node	Soft tissue	CNS	SC or CUT	*other
CO16	106.2+	247	5	0	1			1	
3903	102.7+	853	7	0	1				
H9	86.3+	43	4	0	1				
4578	72.3+	273		0				1	
2364	65.3+	124	1	0	1			3	
6269	61.9+	63		0	3				
8374	59.1+	133	1	0	3				
6803	41.2+	260	2	0	2			2	
7341	40.5+	414	8	0				5	
5373	24.1+	897		0				12	
6483	18.2	100		0	2	1		1	5
5747	12.9	62	6	0				12	1
5454	8.9	129		0	3				
9382	8.3	247	1	2			2		
7525	6.4	182	3	0		1			
495	6.2	57	1	0					
014kc	2.5	123	1	1			3		

+ ongoing responses

* Patient 6483 had renal, perirenal , and periheptic sites designated as "other" disease; Patient 5747 had adrenal metastasis

Table 9- Partial Responders-Duration of response, tumor burden, % regression of tumor, and IL-2 doses

Pt.	Response duration	Tumor burden	"Best response"	"Max" response	cum dose IL-2	IL-2
	months	cm^2	% shrinkage	% shrinkage	MIU/kg	# doses/# courses
CO76	*91.5+*	30.2	62	89	28	47/2
009kb	*54.9+*	49.2	56	67	52.5	97/4
3140	*29.4*	25.3	57	90	20.9	29/2
6923	*18.4*	0.7	69	69	49.7	69/5
6207	*16.8*	7.3	64	88	8.6	12/1
431	*14.0*	100	51	65	15.6	26/1
CO82	*12.5*	25.9	76	98	24.6	41/2
2506	*9.5*	36.8	58	65	18.7	26/2
8455	*8.2*	81.6	58	65	18.7	26/2
2434	*7.4*	20.5	79	82	39.6	55/5
8018[1]	*6.6*	[1]	[1]	[1]	32.4	45/3
7472[2]	*6.4+*	37.7	57	79	25.8	43/2
499	*6.0*	98.8	87	87	39.0	65/3
470	*5.7*	4.4	78	100	33.6	56/2
7433	*4.2*	10	*40	60	46.1	64/4
5165	*3.9*	94.6	53	55	31.7	44/3
9023	*3.8*	5.6	73	73	23.0	32/2
6328	*3.5*	20.1	56	97	27.4	38/3
CO40	*3.4*	76.3	71	71	23.4	39/2
8473	*3.2*	5.0	87	87	11.4	19/2
9056	*3.2*	39.8	56	65	10.2	17/1
5055	*2.1*	32.4	88	95	12.6	21/1
483	*2.1*	69.5	72	72	41.1	69/3
6533	*2.1*	3.8	91	91	28.8	40/2
6960	*2.1*	230.3	57	57	20.2	28/2
439	*1.5*	19.2	59-	59	7.8	13/1

+ ongoing remission

"Cum" refers to the cumulative IL-2 dose

[1]No baseline data was available

2 patient censored at time of alternative treatment ; BMT

*7433 demonstrated a 40% decrease in tumor cross product and should not have been classified PR until 1/26/88 at which time a 60% tumor regession was noted.

Table 10. Partial Responders (n=26) -Duration of response, time from 1st dose IL-2 to "best response", and timelines

Pt. ID#	1st dose IL-2 to "best response"	Date 1st IL-2 dose	Date Best response	Date last IL-2 dose
	days	*date*	*date*	*date*
CO76+	106	10/18/88	2/1/89	2/22/89
009kb+	73	3/27/92	6/8/92	12/16/92
3140	63	4/3/91	6/5/91	6/23/91
6923	79	7/17/90	10/4/90	8/7/94
6207	75	4/10/91	4/10/91	4/29/91
431	241	9/13/88	*5/12/89@*	9/30/88
CO82	37	7/4/89	8/10/89	10/21/89
2506	43	6/2/86	7/15/86	9/23/86
8455	146	3/29/90	*8/22/90@*	7/6/90
2434	98	4/14/86	7/21/86	10/23/87
8018	174	7/14/89	*1/4/90@*	1/4/90
7472+	43	1/31/88	3/14/88	5/23/88
499	48	8/20/90	10/7/90	4/28/91
470	50	5/30/89	7/19/89	9/22/89
7433	89	9/30/87	12/28/87	10/24/88
5165	144	7/12/91	12/3/91	2/13/92
9023	61	10/9/91	12/9/91	1/30/92
6328	60	8/30/86	10/29/86	4/14/87
CO40	87	6/29/87	9/24/87	10/28/87
8473	153	12/15/87	*5/16/88@*	3/13/88
9056	46	2/23/88	*4/9/88@*	3/9/88
5055	44	11/16/87	*12/30/87@*	12/2/87
483	23	2/13/90	3/8/90	11/9/90
6533	66	9/22/90	11/27/90	12/3/90
6960	68	7/13/90	9/24/90	10/20/90
439	42	11/8/88	12/20/88	11/13/88

@ "Best response " was after last dose of IL-2 in these 6 patients.
In 20/26 PR IL-2 therapy continued while in partial remission

Organ-specific pattern of responses. Responses were observed in patients with both visceral and non-visceral sites of metastases. The distribution of metastatic tumor sites is shown in tables 8 (CR) and 13 (PR). Among patients achieving complete responses, the majority had disease limited to pulmonary, nodal, subcutaneous and cutaneous sites, although visceral lesions were present in the liver (2 patients), CNS (1) and adrenal. Pulmonary, nodal, subcutaneous, and cutaneous sites of involvement were also common among patients achieving partial responses, however, marked reduction in tumor volume were observed in hepatic (n=7), adrenal, and renal sites of metastases. Among patients achieving partial responses, tumor regression was usually observed at all sites of disease, however variable degrees of response in different lesions was observed within individual patients.

The last column in Table 11 identifies those patients in whom every measurable lesion regressed at time of "best response" (denoted by single asterik [*]) while a double asterik [**] indicates that some measurable lesions regressed but others remained stable. The patients with a mixture of responding and stable lesions are as follows: 6923-multiple cutaneous lesions were stable while 1 large cutaneous lesion regressed; 6207- 2 liver lesions were stable while a lung and a liver lesion regressed; CO82 -one SC lesion did not regress; 470- 1 lymph node was stable and other regressed; 9023-2 liver lesions regressed while 1 lymph remained stable; 6960-1 lymph did not regress while multiple lymph and SC lesions and one kidney lesion did.

Table 11. Partial Responders: distribution and number of lesions by organ site

Pt. ID #	Lung	liver	lymph node	Soft tissue	CNS	SC or CUT	other	Lesion Regression
	number of sites of disease							
CO76+	6	11	13				1	*
009kb+	4	2						*
3140	6		1			3		*
6923						11		**
6207	1	3			2			**
431							1adrenal	*
CO82	2		1	3		3	1	**
2506	1	2					1	*
8455			2					*
2434						8		*
8018						6		*
7472+		4				2		*
499	1		4	2		2		*
470			2					**
7433						1		*
5165	1		1			1		*
9023		2	1					**
6328	4		1			2		*
CO40			4			6	1adrenal	*
8473			3					*
9056		4	1					*
5055	1		1		1	1		*
483			2			6		*
6533						7		*
6960			2			6		**
439			1			1		*

Dose-response relationship Patients who received a greater number of courses of IL-2 also had a higher response rate, however, since continuation of treatment was dependent, on the treatment outcome, including lack of evidence of disease progression one cannot conclude that there is a dose-response relationship. The studies were not designed to address optimal dose or evaluate a dose-response relationship. There were 118 patients who received the 600,000 IU/kg dose and 147 patients who received 720.000 IU/kg. The median cumulative IL-2 dose delivered was similar in studies utilizing the

two doses (720,000 IU/kg and 600,000 IU/kg). The ORR in the three studies which utilized the 600,000 IU/kg dose were 11%, 13%, and 17% with a median duration of response of 7.2 months and median PFS of 8.3 months. The ORR was similar in the 3 studies which utilized the 720,000 IU/kg dose (14%, 17%, and 16%), with slightly longer median duration of response, 12.9 months, and median PFS, 14.9 months. Among the 43 responding patients, 20 received the 600,000 IU/kg dose and 23 received the 720,000 IU/kg dose. Based on the data submitted, the minimum effective dose has not been established and there is no clear indication of a dose-response relationship.

Tumor burden. Comparative median tumor burdens are shown below. Data regarding tumor burden at baseline was not recorded for all patients in all eight studies (in some studies, baseline and serial tumor measurements were maintained in the database only for responding patients). Among responding patients, there were subjects with multiple lesions and with individual lesions of large size. The total tumor burden (measured in cm^2) was higher in the subgroup achieving a PR as compared to those achieving CR. However the median tumor burden for patients achieving CR and those who failed to respond were similar.

Table 12. Median Tumor Burden

Response	Evaluable/Total #	Median cm^2 (Range)
CR	15/17	17 (3-12)
PR	25/26	29 (1-230)
NR	91/227	20 (.2-432)

Partial responders were evaluated for the degree of tumor regression. Only a limited number (16 of the 25 patients with data) had more than 70% tumor regression.

Table 13 . Regression of tumor in Metastatic Melanoma

Percent shrinkage of tumor	Best response n=270 (%)	"Maximum response" n=270† (%)
90% or >	18 (7%)	24 (9%)
80-89%	3 (1%)	5 (2%)
70-79%	6 (2%)	4 (1%)
60-69%	4 (1%)	6 (2%)
50-59%	10(4%)	3 (1%)

† PR 8018 lacked baseline data and was unevaluable; 25 PR patients were evaluable.

Factors related to tumor response

No variables were prospectively identified for evaluation of clinical protocols. Retrospective analyses using logistic regression to model main effects and interactions between factors were performed, and results expressed as odds ratios with the 95% confidence intervals (C.I). Only ECOG status PS 0, lack of prior systemic therapy and an increased number of courses of IL-2 therapy were correlated with a higher response rate.

ECOG performance status and response to IL-2 The response rate in patients with ECOG PS 0 at baseline 0 was higher than for those with ECOG PS 1 or 2. Among the 191 patients with ECOG PS 0, there were 14 CRs (7%) and 22 PRs (11.5%) as compared to the 74 patients with ECOG PS 1 and 5 patients with ECOG PS 2, in whom 4 CRs (4%) and 5 PRs (5%) were reported.

Prior systemic treatment and response to IL-2 Patients without a history of prior systemic therapy, which comprised approximately half the study population, had higher response rates (21% ORR vs. 10% ORR).

TABLE 14. FACTORS ASSOCIATED WITH RESPONSE

Variable	Comparison	Response Rate	Odds Ratio (95% CI)
Age	>40 yrs	15% (22/147)	0.86
	≤40 yrs	17% (21/123)	(0.44, 1.65)
Gender	males	15% (26/174)	0.82
	females	18% (17/96)	(0.42, 1.62)
Visceral involvement	Yes	14% (26/186)	0.64
	No	20% (17/84)	(0.33, 1.28)
ECOG PS	ECOG PS ≥1	9% (7/79)	0.42†
	ECOG PS 0	19% (36/191)	(0.16-0.93)
Prior systemic therapy†	Yes	10% (12/123)	0.41†
	No	21% (31/147)	(0.19, 0.81)
No. of metastatic sites	>1 site disease	17% (33/191)	1.44
	1 site disease	13% (10/79)	(0.69, 3.23)

† **significant**

SECTION SIX-INTEGRATED SAFETY SUMMARY

Adverse events. Ninety five percent of patients experienced grade 3, and 35% experienced grade 4 adverse events (AE) during IL-2 treatment in these 8 studies. AE data are presented both in a combined format is table 15 in column 2 (RCC+MM) showing all grades for AE > 10% in incidence, for MM alone showing all grades for AE > 10% in incidence (column 3) and for MM grade 4 only (column 4). Major AE in both RCC and MM studies were comparable. No new AE findings were encountered in these studies.

The study patients who received the lower dose schedule (600,000 IU/kg) appear to have tolerated the IL-2 better as evidenced by a higher mean number of doses/patient (22) as compared to 16 for the higher dose (720,000 IU/kg) studies. However, very few patients received 28 doses/course.

Multiple AE were often encountered in the same patient and within the same timeframe. One frequent clinical picture was of hypotension requiring blood pressure support, decreased urinary output and pulmonary congestion/dyspnea. Cardiac problems, including both arrhythmias and thrombosis, and gastrointestinal problems, ranging from diarrhea and vomiting, to liver function test abnormalities, were also frequent. A clinical picture of sepsis was encountered in the majority of aldesleukin- related deaths. Many of the clinical symptoms were similar to, and possibly related to lymphokine release/ capillary leakage syndromes and gram negative sepsis. It has been suggested that a common denominator of the wide spectrum of toxicities affecting blood pressure, renal function, cardiovascular function, the lungs and the gastrointestinal system and in some instances resembling infection is hypoperfusion. Based on experience with catheter-related sepsis prophylactic antibiotics are used in patients with metastatic renal cell carcinoma treated with IL-2.

Table 15. Adverse events

Body System	RCC & MM n=525	MM n=270
	% of patients	% of patients
Body as a whole		
chills	52	40
fever	29	21
malaise	27	34
asthenia	23	
infection	13	15
pain	12	
abdominal pain	11	
abdomen enlarged	10	
Cardiovascular		
hypotension	71	64
tachycardia	23	
vasodilatation	13	
supraventricular tachycardia	12	17
cardiovascular disorder	11	19
arrhythmia	10	
Digestive		
diarrhea	67	54
vomiting	50	55
nausea	35	24
stomatitis	22	14
anorexia	20	
nausea and vomiting	19	
Hemic and Lymphatic		
thrombocytopenia	37	43
anemia	29	29
leukopenia	16	21
Metabolic and Nutritional		
bilirubinemia	40	51
creatinine increased	33	35
peripheral edema	28	31
SGOT increased	23	39
weight gain	16	
edema	15	
acidosis	12	
hypomagnesemia	12	
hypocalcemia	11	
alkaline phosphatase increased	10	13
Nervous		
confusion	34	30
somnolence	22	17
anxiety	12	
dizziness	11	
Respiratory		
dyspnea	43	31
lung disorder	24	
respiratory disorder	11	13
cough increase	11	
rhinitis	10	

Body System	RCC & MM n=525 % of patients	MM n=270 % of patients
Skin and Appendages		
rash	42	27
pruritus	24	
exfoliative dermatitits	18	15
Urogenital		
oliguria	63	49

The following life-threatening (grade 4) adverse events occured in less than 10% of the patients: oliguria (9%), anuria (8%), respiratory (4%), cardiovascular disorders (3%), diarrhea (3%), vomiting (3%), psychosis (2%), infection (2%), hyperbilirubinemia (2%), myocardial infarction (1%), ventricular tachycardia (1%), sepsis (1%), hypotension (1%), dyspnea (1%), neuropathy (1%), stupor (1%), thrombocytopenia (1%), transaminase elevation (1%), fever (1%), rigors (1%). The following grade 4 events occurred in less than 1% of the study population: acute renal failure, coma, AV block, myocardial ischemia, atrial arrhythmia, pancreatitis, pulmonary edema, pneumothorax, anemia, leukopenia, stomatitis, hypocalcemia, elevated alkaline phosphatase.

The spectrum and severity of AE observed across the 8 studies were comparable. Data on irreversible grade 3 and 4 AE and serious AE's requiring prolonged hospitalization. There was one death among the 147 patients treated on the intramural (NCI) studies (0054, 0097, 0053, 0094). The two multicenter studies had the other 7 deaths.

Incidence of Serious Adverse Events, Deaths, and Withdrawals by Study

	0524	0097	0053	0094	0063	70002	0170	29106	combined
Number of patients	28	84	32	3	9	45	64	5	270
% Grade 3 AE	86%	96%	91%	100%	100%	100%	95%	100%	95% (257/270)
% Grade 4 AE	18%	24%	6%	33%	44%	31%	56%	40%	35% (94/270)
Deaths[1]	0	1	0	0	0	3	4	0	8
Serious AE	0	3	0	0	3	9	15	1	31
Early termination[2]	0	2	0	1	4	2	11	2	22

Serious Adverse events (SAE).

There were 31 events reported in 28 (10%) patients study. The most frequently reported SAEs were cardiovascular abnormalities and infections. Ten of the 31 SAE's were cardiac toxicities including 3 myocardial infarctions. There were 9 episodes of sepsis and 6 of respiratory failure.

Table 15. Serious Adverse Events

Study	Patient	Grade	Related to IL-2	Event
0097	1922506	3	definite	Two episodes of bradycardia one of associated with hypotension
	1912434	4	possible	Bowel perforation associated with peritonitis
	2470937	4	definite	Dyspnea with cough and hyperventilation, hypoxia , requiring intubation
0063	800431	3	definite	Myocardial infarction (B.P. normal)
	863454	4	possible	Myocardial infarction
	886715	3	na	Sepsis and coagulopathy
0170	N1350295	5	na	Infection leading to death.
	N1350295	5	possible	Hepatic & renal insufficiency
	N1350295	5	possible	Myocardial infarction
	CO43	4	possible	Sepsis- S. Aureus
	H5	4	probable	Hepatic encephalopathy
	H8	4	possible	Hyperkalemia, acidosis, oliguria
	E180206483	2	probable	Optic neuritis
	H10	5	probable	Pneumonia with S. Aureus
	N1339382	na	possible	Atrial arrhythmias
	N1338235	na	possible	Bradycardia while on pressors
	N1337902	na	possible	Cardiac arrhythmia- not further characterized
	N053308223	na	definite	Anuria , later development sepsis
	H4	na	possible	Arrhythmias while on presors (dopamine)
	CO76	na	probable	Catheter sepsis
	HO13	na	definite	Hepatic toxicity with bilirubinemia, and grade 4 rash
70002	401	4	probable	Confusion/disorientation, dyspnea, oliguria
	401	4	possible	Bowel perforation
	441383478	3	possible	Pancreatitis
	450	5	probable	Pneumonia (enterococcus), dyspnea, hypotension, oliguria
	8949869	3	probable	Cholecystitis
	KN-491	5	probable	Gram positive septicemia
	141222083	na	probable	Cardiotoxicity
	460	na	probable	Bronchospasm, wheezing, pulmonary infiltrates
	478	na	probable	Heart failure
29106	304	4	definite	Respiratory insufficiency

Deaths of patients on study:

Eight patients died during the study; in two cases was attributed to progressive disease and in six to the IL-2 therapy. Five of the 6 deaths occurred in ECOG PS 1 patients who were 27% of study population and 1 death was in an ECOG PS 0 subject. (ECOG PS 0 patients comprised 71% of study population). The six aldesleukin-related deaths are summarized below:

Protocol 0170, patient EO53308223: 59 year old male with metastatic melanoma began Proleukin in April 1988 and received 14 doses during cycle 1 and 7/14 doses in cycle 2 of first course. After start of cycle 1 he became anuric and was induced to diurese with Lasix and Dopamine. He became oliguric several days later and again recovered with treatment. The second cycle was completed and patient discharged. He was re-admitted and died with both sepsis and recurrent disease 37 day days after start of Proleukin.

Protocol 0170, patient H10: A 36 year old female with metastatic melanoma began Proleukin in April, 1989 receiving 11 doses. At time of the last dose, S. aureus and S. epidermis bacteremia were diagnosed. Central venous line was removed and antibiotics begun. There was progressive confusion, hypoxia, pulmonary infiltrates and pulmonary failure. Death was approximately 40 days after the first IL-2 dose.

Protocol 0170, patient N1350295: A 54 year old male had metastatic melanoma involving subcutaneous tissue, liver and lungs. After a first cycle of 14 doses of IL-2, there was hepatic and renal insufficiency characterized by confusion , acidosis, and a small myocardial infarction. Later developments included S. aureus septicemia , bowel infarction, pneumonia, hypotension, hypoxemia and death.

Protocol 70002, patient E404: A 40 year old female with metastatic melanoma involving right axilla and liver. On admission, liver chemistries were elevated. In the first cycle she received 13 doses and in second cycle 9 /14 intended doses. After her last dose, fever, hepatic encephalopathy, S. Aureus septicemia developed. Patient expired 7 days after last dose.

Protocol 70002, patient E450: A 58 year old female with metastatic melanoma who received 14 doses in a first cycle complicated by oliguria managed with fluid administration. Later the patient developed respiratory distress and low arterial oxygen (60%). Chest xray showed pulmonary edema progressing to ARDS. Urine was positive for Klebsiella. After improvement the patient again became hypotensive and febrile. Pneumonia was diagnosed . Sputum was positive for enterococcus. Slow deterioration continued with fevers, ARDS, decreasing renal function. Death was a month later.

Protocol 70002, patient E491: A 56 year old female with metastatic melanoma. During the first course she received 20/28 intended doses. 24 hours after the last dose, the patient became hypotensive requiring pressor support. Blood cultures grew gram positive cocci. Death occurred within 24 hours of last dose of Proleukin.

Early Termination from study

Twenty two patients terminated from study within the first 30 days. The reasons for yearly termination provided in the application were toxicity (n=16), patient refusal to continue treatment (n=5), and withdrawal to receive alternative therapy (n=1). 14/22 were ECOG 0 and 8 ECOG 1. The toxicity related patients included grade 4 oliguria, grade 3 malaise, grade 2 arrhythmia, grade 3 dyspnea, grade 2 alopecia, grade 3 vomiting. The two permanent AE sequelae were a myocardial infarction and ischemic necrosis requiring an amputation. The 16 toxicity-associated early terminations are seen below.

Table 16 - Early terminators from study for toxicity

Patient	Protocol	AE	Grade AE	IL-2 related	Sequelae
1922506	0097	Arrhythmia, hypotension, respiratory disorder	3 3 4	yes	recovered
2470937	0097	respiratory disorder	4	yes	recovered
800431	0063	myocardial infarction	4	yes	recovered
863454	0063	myocardial infarction	4	yes	Alive - unknown sequelae
908473	0063	paraesthesia	3	yes	Paraesthesia ongoing
CO43	0170	bacterial sepsis empyema. respiratory disorder	4 4 4	yes	Patient required intubation Recovered
CO76	0170	oliguria ischemic necrosis	4 4	yes	no data

		respiratory disorder	4		
E132169056	0170	hepatitis B	na	yes	contaminated plasminate
E180206483	0170	optic neuritis	2	yes	recovered
H4	0170	arrhythmias anuria cardiac disorder	2 4 3	yes	arrythmias related to Dopamine & IL-2
H5	0170	encephalopathy respiratory disorder	4 4	yes	recovered
H8	0170	hyperkalemia	4	yes	recovered
H13	0170	hyperbilirubinemia thrombocytopenia oliguria	4 4 4	yes	recovered
E460	70002	pulmonary edema asthma	3 3	yes	recovered
E478	70002	cardiomyopathy anuria	2 4	yes	recovered
011RM	9106	respiratory insufficiency	2 3	yes	recovered

Additional studies. Nine trials which employed aldesleukin either by continuous infusion or subcutaneously or using dose different dose schedules than the 8 integrated studies were reviewed. Data were provided by individual study to support safety. Inspection of AE showed they were similar to those encountered in the integrated studies although the incidence of grade 3 or 4 AE varied widely. No unusual or unexpected toxicities were encountered.

Immunology. Sera from 50 patients with melanoma, treated with single agent aldesleukin, were analyzed for the presence of IgG and IgM antibodies to Proleukin by ELISA. Patient sera was collected and sent to Chiron on dry ice and stored at 20 degrees C until assay. All patients had a pretreatment sample. Titers over 10 were considered positive. Sixty-six percent (33/50) of the patients developed antibodies after IL-2exposure. Most of the titer levels were low, however 14% (7/50) of samples had titers $\geq$100. Four of these high titer patients were enrolled in a trial which used a two week continuous infusion combined with twice a day one hour infusions of IL-2. In the majority of patients, titers decreased after cessation of therapy or during subsequent courses of therapy. This data is similar to the results observed in the renal cell carcinoma population, where 74% of patients (57/77) developed positive ELISA titers, (Sec 5.4 volume 6). In the immunology section of the application it is noted that the samples were kept at 20 C until assay and there may be concern that at this temperature the titer and the number of positive patients may be underestimated.

SECTION SEVEN-REVIEWERS COMMENTS

Two hundred and seventy patients with metastatic melanoma were treated with either 600,000 or 720,000 IU/ kg of aldesleukin by short intravenous/bolus infusions in eight studies over an 8 year period (1985-1993). The objective response rate for the 270 patients was 16% with 26 partial responses (10%) and 17 complete responses (6%). Ten CR patients have remained in remission for more than 2 years; median duration of CR has not been determined. In contrast, median duration of PR is 5.9 months;

Safety was based on the 270 subjects in the integrated studies, plus limited information from 268 patients given IL-2 by other routes/other doses, and data from 255 renal cell carcinoma patients IL-2. The high incidence of severe adverse events(AE), grade 3 AE were seen in 95% of subjects and grade 4 AE in 35% of patients, were similar in severity and AE to those observed earlier in patients with renal cell carcinoma (see table 15). A clinical grouping of hypotension, which could require pressors, anuria and oliguria and pulmonary symptoms, were noted. There was serious cardiac toxicity including arrhythmias and myocardial infarction, and a high frequency of nausea, vomiting, and liver chemical abnormalities. There were 28 serious adverse events (SAE) in 10.4% of patients. Six of 270 patients had aldesleukin-related deaths (2.2%); evidence of significant organ dysfunction (pulmonary, hepatic, and/or renal) and/or infection appeared to be the underlying causes of death.

CBER analysis by CBER focused on four areas:

(a) *The consistency of the integrated database across the 8 studies;*

(b) *Initial definition of patient population;*

(c) *Delineation of prognostic factors for treatment effect;*

(d) *Clinical value of responses.*

In addition, the present results were compared to the published results to alternative therapies available and in use for the treatment of metastatic melanoma.

(a) The 8 studies entered in the integrated database were performed from 1985 through 1993. All were phase 1 or 2 studies and all were addressed, in the main, to establishing dose and administration route criteria. Medical practices and the treatment of complications of IL-2 therapy and melanoma were evolving during the 8 year drug development period. Comparison of the 8 studies to each other, as far as available data allowed, suggest similar experimental formats and patient demographics and more importantly reasonably comparable tumor responses and safety profiles across studies. The degree of comparability is attributable in part to the relatively straightforward dose and administration patterns employed and to toxicity driven dosing, factors in common to all 8 studies.

(b). Eligibility criteria required only a diagnosis of metastatic melanoma which had failed standard therapy and had measurable lesions. Approximately one-quarter of the patients had disease limited to nodal, cutaneous or subcutaneous sites. In sufficient information was provided to permit a determination of whether patients could have had regional nodal recurrence or in-transit metastases (stage III disease), which would be expected to result in better response and survival than than for stage IV patients. However, among the responding patients, there was only one patient with a single site of cutaneous disease, with a lesion volume of 10cm^2, whereas the remainder had between 6-12 sites of subcutaneous and/or cutaneous disease and 2-3 nodal sites of involvement, thus it is unlikely that these subjects would have been appropriate candidates for surgical intervention. In addition to lack of staging information, detailed information on prior therapy and response to prior therapy was deficient. Immunotherapy was a major treatment modality but no description of the type of immunotherapy, details regarding response and the length of clinical responses were provided. Clear definitions for treatment failure were not provided in the clinical protocols (as it would relate to eligibility). Finally, there was a lack of detailed data on the length and natural history of disease including date of diagnosis, and date of first metastatis which could have provided insight into the clinical aggressiveness of the disease in the study population.

In contrast, very useful data in defining the population was collected on incidence of visceral lesions(69% of study population) and the incidence of 2 or more sites of disease (71% of study population). Both of these factors have been reported to be associated with a poor prognosis. These latter data suggest that most of the study group had advanced metastatic melanoma; however given the lack of certain information, one cannot rule out that patients with more indolent disease were enrolled and that the survival and PFS results reflect a more benign natural course rather than an IL-2 induced treatment effect.

(c) Prospective analyses to delineate the variables influencing treatment effect such as age, sites of lesions, length of time between primary and metastatic disease and therapy, dosage were not initially part of the 8 studies. Retrospectively collected data indicated there was an improved response rate and decreased number of deaths in ECOG 0 vs. ECOG PS 1 patients, -as noted for the earlier renal cell carcinoma studies. Although there also appeared to be correlation's between a higher response rate and lack of prior systemic therapy and an increased number of IL-2 courses/patient, all of the correlation's can be explained by assuming that all three above factors reflect a better health status of the patient and perhaps less advanced disease and ability to tolerate more drug. The present information is not able to distinguish those patients in whom a physician could anticipate maximum benefit and least toxicity from the proposed therapy, except to reinforce the observation noted in the renal cell studies linking ECOG status to response.

If this supplement is approved, consideration should be given to reviewing and reinforcing the already strong labeling on patient entry status. Five of 6 deaths were in ECOG PS 1 patients who were only 27% of the study population. On the other hand only 8% of 6/74 ECOG PS 1 subjects had objective responses.

(d). The clinical utility of the above aldesleukin regimen for MM can be judged in terms of overall success rate, the "durability" of the objective responses that were obtained, and the quality of life impact of therapy on both responders and non-responders. The OR is within the range described for DITC , the most widely employed single agent regimen, as well as interferon and other single agents. Combination therapies report higher remission rates but they may be of short duration and toxicity is anticipated to be greater than for single agents. Thus IL-2 would offer an alternative treatment modality. The OR rate included many PR with relative short durations of remission. Tables 8 and 9 in the last part of Section 5 lists the percentages of patients with duration of response over various times. The last entry indicates 8.9% of patient had over a 7 month response duration(CR are 14 patients , PR are 10 patients). If the duration of response is over a year the percentage drops to 7% and so on. The relatively longer responses are only 5-10% of the study population and mainly CR. This compares unfavorably to the data from RCC in which the average PR duration was on follow-up 20 months. Likewise table 13 indicates that the regression of the tumor mass is less dramatic in these MM patients than for RCC.

The level of toxicity is very high with almost all patients having grade 3 and a third having grade 4 toxicity. A consequence is the inability of most patients to receive the full course, that is the maximum 28 doses of IL-2. Analysis of data on dates of first and last IL-2 therapy, seen in table 10 , shows that most PR patients had their last IL-2 treatment after remission (PR) was declared. For the substantial number of PRs of short duration (table 9) , the need for further IL-2 treatment with its attendant hospitalization for 10-20 days, and toxicity makes the remission less advantageous. The 84% of non responders were also subjected to substantial toxicity and discomfort without any benefit.

The major advantage of the proposed regimen for MM is its durability, which, despite the limited numbers, is substantial when present. Among the 43 responders 17 were still alive with a 5 year follow-up. The remission data, as well as the late and ongoing character of some of the responses, imply an anti-tumor activity which differs from other agents now used and, with modifications or in combination,will find further uses.

SUBMITTED,

1/6/98

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